Randomized Trial of Simple Versus Complex Drug-Eluting Stenting for Bifurcation Lesions

The British Bifurcation Coronary Study: Old, New, and Evolving Strategies

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Background—The optimal strategy for treating coronary bifurcation lesions remains a subject of debate. With bare-metal stents, single-stent approaches appear to be superior to systematic 2-stent strategies. Drug-eluting stents, however, have low rates of restenosis and might offer improved outcomes with complex stenting techniques.

Methods and Results—Patients with significant coronary bifurcation lesions were randomized to either a simple or complex stenting strategy with drug-eluting stents. In the simple strategy, the main vessel was stented, followed by optional kissing balloon dilatation/T-stent. In the complex strategy, both vessels were systematically stented (culotte or crush techniques) with mandatory kissing balloon dilatation. Five hundred patients 64±10 years old were randomized; 77% were male. Eighty-two percent of lesions were true bifurcations (>50% narrowing in both vessels). In the simple group (n=250), 66 patients (26%) had kissing balloons in addition to main-vessel stenting, and 7 (3%) had T stenting. In the complex group (n=250), 89% of culotte (n=75) and 72% of crush (n=169) cases were completed successfully with final kissing balloon inflations. The primary end point (a composite at 9 months of death, myocardial infarction, and target-vessel failure) occurred in 8.0% of the simple group versus 15.2% of the complex group (hazard ratio 2.02, 95% confidence interval 1.17 to 3.47, $P=0.009$). Myocardial infarction occurred in 3.6% versus 11.2%, respectively ($P=0.001$), and in-hospital major adverse cardiovascular events occurred in 2.0% versus 8.0% ($P=0.002$), respectively. Procedure duration and x-ray dose favored the simple approach.

Conclusions—When coronary bifurcation lesions are treated, a systematic 2-stent technique results in higher rates of in-hospital and 9-month major adverse cardiovascular events. This difference is largely driven by periprocedural myocardial infarction. Procedure duration is longer, and x-ray dose is higher. The provisional technique should remain the preferred strategy in the majority of cases.

Clinical Trial Registration Information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT 00351260.

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Key Words: coronary disease ■ bifurcation ■ stents ■ angioplasty

Coronary bifurcation lesions were considered high risk for angioplasty in the early interventional era because of higher rates of dissection, myocardial infarction, and acute vessel closure.[1] The advent of coronary stenting reduced the risks, but in-stent restenosis was noted to be frequent at the ostium of the side branch.[2] Two-stent techniques were developed to try to combat this phenomenon[2,3] but gave inferior results to the provisional T technique in nonrandomized

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studies.[4,5] For bare-metal stents, therefore, the provisional T-stent strategy was considered to be the gold standard approach.[6]

Clinical Perspective on p 1243

The introduction of drug-eluting stents restored interest in more complex bifurcation techniques because of the extremely low observed rates of restenosis.[7] The crush and culotte techniques, respectively, were developed[8] or refined[9] to improve outcomes.

Early studies into the use of drug-eluting stents at bifurcations were reasonably encouraging.[10,11] We therefore designed a randomized trial to compare the provisional T-stent strategy with a systematic 2-stent technique using drug-eluting stents.

Methods

The study was an investigator-led prospective, randomized, multicenter trial in the United Kingdom and was funded through the Cardiac Research Unit at the Sussex Cardiac Centre (including unrestricted research funding from Boston Scientific) and through a grant from the Brighton and Sussex University Hospitals NHS Trust. The study protocol was approved by the UK National Research Ethics Service and the Medicines and Healthcare Products Regulatory Agency.

Study Population

Patients were eligible for the study if they were at least 18 years old and had bifurcation coronary artery disease that required percutaneous coronary intervention (PCI) in which the main-vessel reference diameter was ≥2.5 mm and the side-branch reference diameter was ≥2.25 mm. Main exclusion criteria were unprotected left main stem narrowing ≥50%, primary angioplasty for acute ST-elevation myocardial infarction, cardiogenic shock, chronic total occlusion of either vessel, additional type C or bifurcation lesion that required PCI, left ventricular ejection fraction ≤20%, platelet count $\leq 50\times10^9/mm^3$, patient life expectancy <12 months, or known relevant allergies. Patients who consented to participate in the study were randomized via a secure World Wide Web site by use of standard random-number-generation methodology with stratification by center.

Revascularization Procedure

Pre-PCI

Patients were assessed for angina status (Canadian Cardiovascular Society) and antianginal medication. Aspirin 75 mg/d was continued if the patient was established (>3 days) on this medication. If not, aspirin 300 mg was given ≥3 hours before PCI. Clopidogrel 75 mg/d was continued if the patient was established (>3 days) on this medication. If not, clopidogrel 600 mg was given ≥3 hours before PCI. Intravenous unfractionated heparin 70 IU/kg was given at the start of the procedure and to keep the activated clotting time ≥200 seconds during the procedure. Glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator. Blood for serum creatine kinase (CK) and troponin levels was taken at the start of the procedure.

Percutaneous Coronary Intervention Procedure

PCI was undertaken via the access site of choice of the operator. TAXUS paclitaxel-eluting stents (Boston Scientific Corp, Natick, Mass) were used. Only operators with a minimum annual volume of 150 cases were allowed to participate.

Simple Group

Patients randomized to the simple arm of the study underwent a provisional T-stent strategy with strict rules for progression through each stage.

Stage 1. Coronary guidewires were passed to the main vessel and, where desired, the side branch. The main and side vessels were pretreated at the operator's discretion. The main vessel was stented with or without wire protection of the side branch according to operator preference. The side branch was not treated further unless there was Thrombolysis In Myocardial Infarction (TIMI) flow <3 in the side branch, severe ostial pinching of the side branch (>90%), threatened side-branch vessel closure, or side-branch vessel dissection greater than type A. If 1 of these criteria existed, the operator could progress to the next stage, but this was not mandatory.

Stage 2. The side branch was rewired, and a kissing balloon inflation was undertaken with anatomically appropriate sizing for each vessel. The side branch was not then treated further unless there was TIMI flow <3 in the side branch, persistent ostial pinching of the side branch (>70%), threatened side-branch vessel closure, or side-branch vessel dissection greater than type A.

Stage 3. If 1 of these situations applied, T stenting of the side branch could be undertaken, with mandatory kissing balloon inflation.

Complex Group

Patients who were randomized to the complex arm of the study underwent a crush or a culotte procedure according to operator preference.

Crush Technique. Both vessels were wired, with lesion preparation as for the simple strategy. For a 6F guiding catheter approach, a stent in the side branch was positioned adjacent to a balloon in the main branch. With 7F/8F guiding catheters, 2 stents could be placed simultaneously. The side-branch stent was deployed first, with struts overhanging into the main vessel to ensure full coverage of the side-branch ostium. After removal of the side-branch wire and balloon, the main vessel was ballooned and stented sequentially (6F) or stented (7F/8F). The side branch was rewired, and a mandatory attempted kissing balloon dilatation was undertaken to optimize stent-to-wall apposition.

Culotte Technique. Both vessels were wired, with lesion preparation as for the simple approach. The side branch (or more angulated vessel) was then stented first with a wire jailed in the main vessel. The main vessel was rewired through the stent struts, dilated, and (after withdrawal of the side-branch wire) stented. The side branch was rewired, and mandatory attempted final kissing balloon inflations were undertaken.

For both groups, at any stage, proximal or distal dissections could be treated with further stenting. Postdilations could be undertaken to optimize stent expansion. In all cases, an additional vessel with type A or B lesion could be treated if required.

Post-PCI

Hemostatic technique and use of vascular closure devices were at the discretion of the operator. When the femoral approach was used, sheaths were removed when the activated clotting time was ≤175 seconds. CK and troponin were taken 16 to 22 hours after PCI. Aspirin 75 mg/d and clopidogrel 75 mg/d were given for a minimum of 9 months.

Follow-Up

Adverse event tracking began at randomization and continued to the end of the 9-month follow-up period. Patients underwent either telephone or hospital follow-up at 3 and 6 months, followed by a final hospital follow-up visit at 9 months. At the 9-month visit, Canadian Cardiovascular Society grade and antianginal medication were assessed.

End Points

The primary end point of the study was a composite of all-cause death, myocardial infarction, and target-vessel failure by 9 months. Secondary end points were the individual components of the primary end point, angina status (Canadian Cardiovascular Society; angina medication score), and repeat angiography at 9 months. Procedural end points were procedural success, completion of final kissing balloon inflations where mandated, in-hospital major adverse cardiovascular events (MACE), in-hospital non-MACE serious adverse events, procedure duration, fluoroscopy time, and x-ray dose.

Table 1. Patient Characteristics and Clinical Features

	Simple (n=250)	Complex (n=250)
Age, y, mean (SD)	64 (10)	64 (11)
Male, n (%)	192 (77)	193 (77)
BMI, kg/m^2, mean (SD)	28 (5)	28 (5)
Diabetes, n (%)	31 (13)	28 (11)
Hypertension, n (%)	142 (57)	154 (62)
Hypercholesterolemia, n (%)	188 (76)	189 (76)
Smoking (current), n (%)	42 (17)	43 (17)
Family history, n (%)	104 (42)	103 (41)
Previous MI, n (%)	57 (23)	63 (25)
Previous PCI, n (%)	42 (17)	40 (16)
Peripheral vascular disease, n (%)	12 (5)	12 (5)
Left ventricular function (%)		
Good (EF >50%)	91	85
Moderate (EF 30–50%)	9	13
Poor (EF <30%)	0	1
Presentation, n (%)		
Elective	170 (68)	161 (64)
Troponin-negative ACS	28 (11)	32 (13)
Troponin-positive ACS	40 (16)	41 (16)
STEMI (convalescent)	11 (4)	16 (6)
Diseased territories >70%, n (%)		
Single vessel	171 (69)	183 (73)
Two vessel	63 (25)	54 (22)
Three vessel	15 (6)	13 (5)
Site of bifurcation disease, n (%)		
LAD	201 (81)	209 (84)
Circumflex	35 (14)	28 (11)
RCA	9 (4)	12 (5)
Other	4 (2)	1 (0)
Bifurcation lesion characteristics, n (%)		
True bifurcation	202 (81)	209 (84)
Type (Medina classification)		
1,1,1	150 (60)	149 (60)
1,1,0	26 (10)	19 (8)
1,0,1	19 (8)	26 (10)
1,0,0	11 (4)	13 (5)
0,1,1	33 (13)	34 (14)
0,1,0	10 (4)	5 (2)
0,0,1	0 (0)	3 (1)
Adverse lesion features, n (%)		
Calcification ≥ moderate	21 (8)	28 (11)
Tortuosity ≥ moderate	25 (10)	27 (11)
Bifurcation angle >60%	38 (15)	32 (13)

BMI indicates body mass index; MI, myocardial infarction; EF, ejection fraction; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; LAD, left anterior descending coronary artery; and RCA, right coronary artery.

Table 2. Procedure Characteristics

	Simple (n=249)	Complex (n=248)	*P*
Access site, n (%)			
Femoral	166 (66)	177 (71)	
Radial	83 (34)	71 (29)	
Sheath gauge, n (%)			
6F	197 (79)	94 (38)	<0.001
7F or larger	52 (21)	154 (62)	
Glycoprotein inhibitor use, n (%)	70 (28)	110 (44)*	<0.001
Before procedure	34 (14)	43 (17)	
During procedure	30 (12)	53 (21)	
After procedure	6 (2)	13 (5)	
Main-vessel lesion			
Mean stent diameter, mm (SD)	3.0 (0.3)	3.2 (0.3)	
Stent length, mm (SD)	21 (6)	22 (6)	
Preprocedure stenosis, % (SD)	87 (10)	85 (11)	
Postprocedure stenosis, % (SD)	3 (13)	4 (16)	
Side-branch lesion			
Mean stent diameter, mm (SD)		2.6 (0.3)	
Stent length, mm (SD)		16 (5)	
Preprocedure stenosis, % (SD)	63 (31)	68 (29)	
Postprocedure stenosis, % (SD)	37 (33)	12 (24)	<0.001
Total stented length, mm (SD)	24 (10)	41 (16)	<0.001
Final kissing balloons			
Attempted, n (%)	76 (31)	223 (90)	
Successful, n (%)	72 (29)	189 (76)	
Success as % of attempted	95	85	0.01

*Timing of glycoprotein inhibitor administration not available in 1 patient.

Definitions

Myocardial infarction: Typical rise and fall of biochemical markers of myocardial necrosis with ischemic symptoms or ECG changes as per European Society of Cardiology/American College of Cardiology guidelines.[12] For patients in the first 24 hours after PCI, CK ≥3 times the upper limit of normal was taken as the cutoff point for the diagnosis of myocardial infarction. For patients who already had a diagnosis of myocardial infarction on the current admission, CK rise to ≥50% of the previous value was used.

Target-vessel failure: This comprised target-vessel revascularization by PCI or coronary artery bypass grafting of either the main vessel or side branch and/or target-vessel inadequacy (TIMI flow <3 in either the main vessel or side branch after appropriate vasodilators on a repeat angiogram, without attempted revascularization).

Procedural success (main vessel): TIMI 3 flow and <30% residual stenosis.

Procedural success (side branch): TIMI 3 flow alone.

Overall procedural success: TIMI 3 flow and <30% stenosis in the main vessel, plus TIMI 3 flow in the side branch.

In-hospital MACE: Death, myocardial infarction, or target-vessel failure during the index admission.

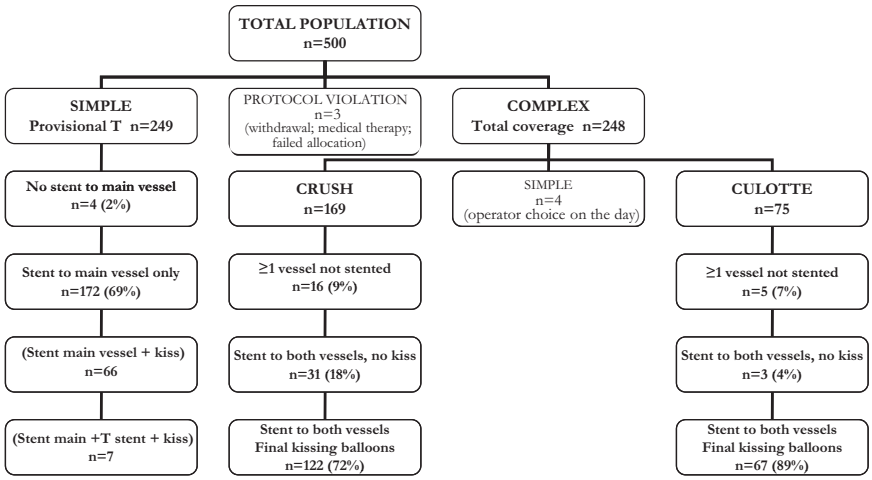

Figure 1. Flow of patients through the trial.

In-hospital serious adverse events (non-MACE): Vascular access surgery, bleeding (TIMI major), and blood transfusion (hierarchical); cardiac tamponade and nontamponade pericardial effusion (hierarchical); stroke and left main stem dissection.

Procedure duration: Time from initial infiltration of local anesthetic to removal of guiding catheter.

Procedure fluoroscopy time: Duration of x-ray utilization.

Diamentor: X-ray dose area product ($cGy \cdot cm^2$).

Angina index: Angina scoring system, scoring 1 for nitroglycerin spray, oral nitrate, β-blocker, calcium antagonist, or nicorandil (maximum score 5).

Medina classification: This classification attributes a score of 0 or 1 to the 3 segments of a bifurcation lesion (proximal main vessel, distal main vessel, and side branch) as a binary function dependent on an angiographic stenosis of >50% (score 1) or <50% (score 0) in each location.[13]

Study Management and Data Collection

The British Bifurcation Coronary study: Old, New, and Evolving strategies (BBC ONE) was overseen by a steering committee. All primary outcome events were reviewed by a clinical events committee. Data were collected from source documentation directly onto a password-protected, encrypted electronic case report form managed by Dendrite Clinical Systems. Data were reviewed twice during the study by a Data Safety Monitoring Board. The principal investigator at each site plus 1 designated research assistant were able to upload and view data solely relating to their own patients. The study statistician gave advice on study design, prepared interim assessments for the Data and Safety Monitoring Board, and performed data analyses. All study sites underwent an initiation visit and a midstudy monitoring visit.

Statistical Analysis

The incidence of death, myocardial infarction, or target-vessel failure was expected to be 20% at 9 months with a simple strategy. A total of 442 patients were required to detect a 50% relative reduction in the primary end point with total lesion coverage provided by the complex strategy, with 80% power and 5% significance. To allow for patients lost to follow-up or protocol violations, it was decided to recruit 500 patients to the study.

The primary composite end point of death, myocardial infarction, and target-vessel failure by 9 months was compared by use of a hazard ratio and 95% confidence interval from a Cox regression model with treatment group as the only covariate. Treatments were compared with a log-rank test and Kaplan–Meier survival curve. Individual components of the primary end point and other secondary end points were summarized by treatment group. Analyses were performed on an intention-to-treat basis with Stata 10.1 software (StataCorp, College Station, Tex).

Results

Between December 2004 and December 2007, 500 patients were randomized to the trial across 21 centers in the United Kingdom and Ireland. One patient withdrew consent before treatment, 1 patient did not undergo attempted treatment, and 1 patient had a temporary failure of electronic randomization, such that 249 patients in the simple group and 248 in the complex group underwent angioplasty. All remained in the intention-to-treat analysis.

Patient demographics and clinical features are shown in Table 1. Procedure characteristics are shown in Table 2. Intervention-related technical aspects of the trial are shown in Figure 1. In the culotte group, 89% of cases had successful completion of the procedure with final kissing balloon inflations, compared with 72% in the crush group. Most failures were due to inability to rewire the side branch successfully (crush n=23/31; culotte n=2/3).

Follow-up to 9 months was complete for vital status in all 500 patients. Two patients were lost to follow-up after the index treatment, but mortality data for these patients were obtained via the Office of National Statistics tracking service. Three patients who did not undergo trial-related intervention had primary end point follow-up but no procedural or secondary end point data. All other patients had complete follow-up.

The primary end point of the study is shown in Table 3. The incidence of death, myocardial infarction, or target-vessel failure was 8.0% in the simple group versus 15.2% in the complex group (hazard ratio 2.02, 95% confidence interval 1.17 to 3.47, $P=0.009$). Cumulative risk of the primary outcome is shown in Figure 2A. Primary end point events are listed in Table 3. The majority of excess events in the complex group were myocardial infarctions. This is shown in Figure 2B, which additionally demonstrates that most myocardial infarctions occurred either during the procedure or soon afterward. Postprocedure cardiac biomarker data were obtained in 93% (CK) and 97% (CK or troponin) of patients, respectively. There was no difference in the rates of target-vessel failure between the 2 groups (Figure 2C), but repeat revascularization in the complex group more frequently involved coronary artery bypass grafting.

In-hospital MACE was more common in the complex group. This is shown in Table 3, which also demonstrates that

Table 3. Trial End Points

	Simple	Complex	Hazard Ratio (95% CI)	*P*
Primary end point	n=250	n=250		
Death, MI, or target-vessel failure at 9 mo (%)	20 (8.0)	38 (15.2)	2.02 (1.17–3.47)	0.009
Secondary end points				
Death (%)	1 (0.4)	2 (0.8)		
Periprocedural (inpatient)	0	1		
Subsequent	1	1		
MI (%)	9 (3.6)	28 (11.2)	3.24 (1.53–6.86)	0.001
Periprocedural (inpatient)	4	17		
Subsequent	5	11		
CK data availability after PCI (%)	233 (94)	231 (93)		
Troponin availability after PCI (%)	233 (94)	222 (90)		
CK or troponin after PCI (%)	244 (98)	240 (97)		
Target-vessel failure (%)	14 (5.6)	18 (7.2)	1.32 (0.66–2.66)	0.43
Stent thrombosis (ARC definite)	1	5		
Restenosis of main vessel only	6	4		
Restenosis of side branch only	6	3		
Restenosis of both	1	6		
Treated with CABG	1	9		
Treated with re-PCI	13	8		
Repeat angiography (%)	32 (13)	43 (17)	1.44 (0.91–2.27)	0.12
In-hospital MACE (%)	5 (2.0)	20 (8.0)	4.00 (1.53–10.49)*	0.002
Death	0	1		
MI	5	18		
CABG	0	3		
Procedural end points	n=249	n=248		
Success in main vessel (%)†	244 (98)	242 (97)		
Success in side branch (%)‡	236 (94)	234 (94)		
Overall procedural success (%)§	235 (94)	234 (94)		
Stent implantation in main vessel (%)	245 (98)	239 (96)		
Stent implantation in side branch (%)	7 (3)	225 (91)		
Procedure time, min, mean (SE)	57 (1.6)	78 (1.9)		<0.001
Fluoroscopy time, min, mean (SE)	15 (0.7)	22 (0.8)		<0.001
Diamentor, cGy · cm^2, mean (SE)	6140 (300)	7900 (350)		<0.001
No. of guidewires used, mean (SE)	2.2 (0.1)	3.1 (0.1)		<0.001
No. of balloons used, mean (SE)	2.3 (0.1)	4.0 (0.1)		<0.001
No. of stents used, mean (SE)	1.2 (0.0)	2.2 (0.1)		<0.001

CI indicates confidence interval; MI, myocardial infarction; CABG, coronary artery bypass graft; and ARC, Academic Research Consortium.

*Risk ratio.

†Defined as TIMI 3 flow and <30% residual stenosis.

‡Defined as TIMI 3 flow.

§Defined as both of the above.

x-ray dose and use of consumables were significantly greater in the complex group. There was a trend toward a higher incidence of in-hospital non-MACE serious adverse events in the complex group (n=10) than in the simple group (n=4). In nonhierarchical analysis, these comprised TIMI major bleeding (complex n=3, simple n=1), blood transfusion (complex n=6, simple n=1), cardiac tamponade (complex n=2, simple n=1), nontamponade pericardial effusion (complex n=3, simple n=1), vascular surgical repair (complex n=0, simple n=1), stroke (complex n=1, simple n=0), and left main stem dissection (complex n=1, simple n=0).

Canadian Cardiovascular Society grade was >2 in 73% of patients before the procedure and improved to 14% in both groups at 9-month follow-up (risk ratio 1.01, 95% confidence interval 0.65 to 1.57). Similarly, the mean (±SD) angina index was 2.06±0.99 before the procedure and 1.38±0.06 at 9-month follow-up, without intergroup difference (simple 1.39, complex 1.37; *P*=0.77).

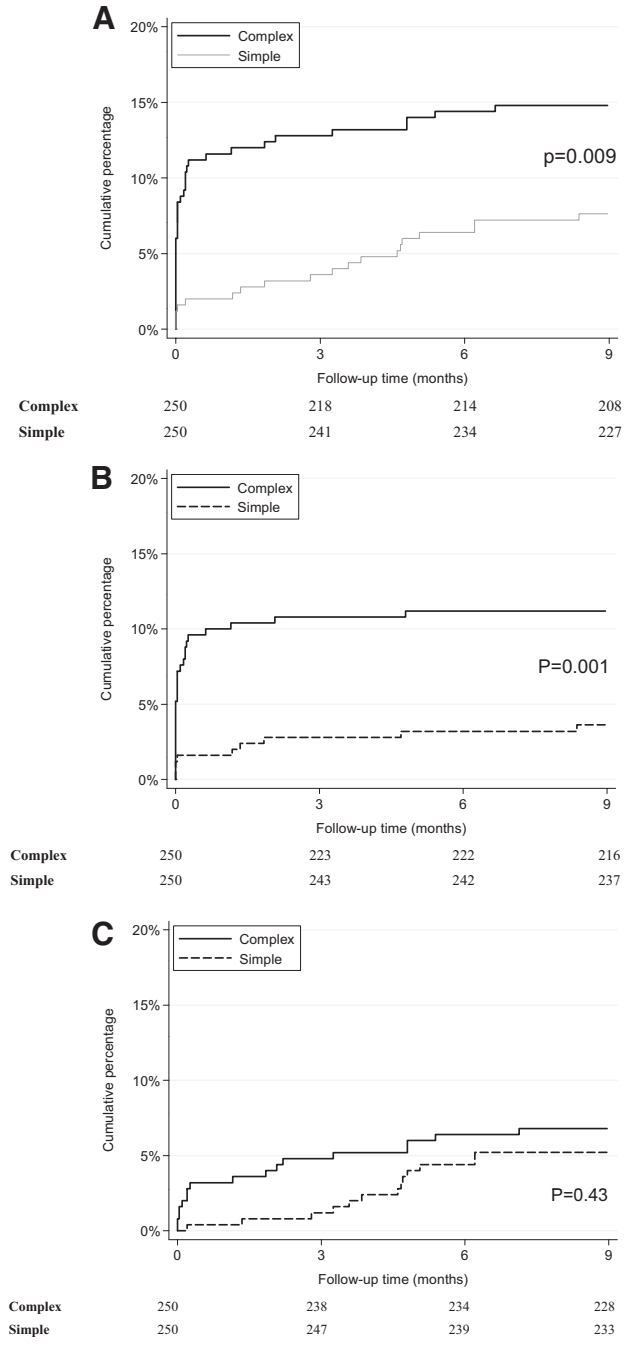

Figure 2. Outcome measures. A, Cumulative risk of primary outcome; B, cumulative risk of myocardial infarction; and C, cumulative risk of target-vessel failure.

Discussion

This large randomized trial of bifurcation stenting strategies has demonstrated that for a side branch of ≥2.25 mm and a main vessel of ≥2.5 mm diameter, a provisional T-stent approach is preferable to a systematic 2-stent strategy. Not only is the more complex procedure disadvantageous periprocedurally but also there is no compensatory "payback" during follow-up to offset and potentially justify the added procedural complexity. Previous studies have shown neither a clear advantage nor a clear disadvantage with more complex strategies, and therefore, the present study is unique in demonstrating a clear difference between the 2 approaches.

Early small randomized studies of bifurcation stenting with drug-coated stents were published in 2004. Colombo et al[11] compared the crush technique with the provisional T strategy. Eighty-five patients were recruited, but there was a high crossover rate such that 73% of patients ultimately had a 2-stent strategy. On angiographic follow-up, there was no significant difference between the 2 groups. This was despite the lack of routine final kissing balloon inflation in the crush stent group, the importance of which was demonstrated the following year.[14]

Pan et al[10] compared a simple strategy of main-vessel stenting and side-vessel dilatation (without kissing inflation) versus a systematic T-stent strategy in 91 patients. There were no statistical differences between the 2 groups after 6 months' follow-up. Ge et al[15] compared the crush and the systematic T-stent techniques in a nonrandomized assessment of 181 patients, two thirds of whom had crush stenting. Ostial side-branch restenosis and target-vessel revascularization at 1 year were both more common in the T-stent group. Ferenc et al[16] also compared the systematic T and the provisional T strategies and found no difference in target-lesion revascularization or ostial side-branch restenosis at 1-year follow-up.

Steigen at al[17] undertook a randomized comparison of main-vessel stenting versus stenting of both the main vessel and side branch (the Nordic Bifurcation Study). A low rate of MACE was seen in both groups at 6-month follow-up (2.9% versus 3.4%, respectively). Periprocedural biomarkers were more frequently elevated to myocardial infarction threshold in the dual-stenting group, but were only obtained in 68% of cases.

There are some important differences between BBC ONE and the Nordic Bifurcation Study. In the present study, biomarker data formed part of the primary end point, whereas in the Nordic Bifurcation Study, periprocedural myocardial infarction was excluded from the primary end point. Periprocedural myocardial infarction, however, may be important as an adverse prognostic indicator,[18] although not all studies have reached the same conclusion in this respect.[19] In the Nordic Bifurcation Study, a number of different complex stenting strategies were used, including T stenting in 29% of cases, which does not provide full lesion coverage. The BBC ONE trial used paclitaxel-eluting stents, whereas the Nordic Bifurcation Study used sirolimus-eluting stents. These stent types have been compared in 2 previous bifurcation studies, both of which suggested that sirolimus-coated stents offer superior results.[20,21]

In the CACTUS study (Coronary bifurcations: Application of the Crushing Technique Using Sirolimus-eluting stents),[22] 350 patients with coronary bifurcations were randomized to crush or provisional T stenting with sirolimus stents. Kissing balloon inflations were mandated in both groups and were achieved in 92% and 90%, respectively. Six-month MACE was similar in the 2 groups (16% versus 15%), and there was no difference in the rate of angiographic restenosis in either the main or side branch. The various randomized studies are shown in Table 4.

The reason for the different primary clinical end point results between the CACTUS and BBC ONE studies may relate to the more aggressive "simple" strategy used in the

Table 4. Randomized Bifurcation Studies

	No. Patients	Randomization	Primary End Point	Outcome (Provisional vs Systematic Unless Otherwise Specified)
NORDIC	413	Provisional vs systematic (crush, culotte, T)	Death, MI (nonprocedural), TVR, or stent thrombosis at 6 mo	2.9% vs 3.4% (P=NS)
CACTUS	350	Provisional vs systematic (crush)	Death, MI, TVR at 6 mo	15% vs 15.8% (P=NS)
BBC ONE	500	Provisional vs systematic (crush, culotte)	Death, MI, TVF at 9 mo	8.0% vs 15.2% ($P<0.05$)
Ferenc et al	202	Provisional vs systematic (T)	Angiographic restenosis (side branch) 9 mo	23.0% vs 27.7% (P=NS)
Colombo et al	85	Provisional vs systematic (crush, T, culotte)	Angiographic restenosis (either branch) 6 mo	18.7% vs 28.0% (P=NS)
Pan et al	91	Provisional vs systematic (T)	Angiographic restenosis (either branch) 6 mo	7% vs 25% (P=NS)
NORDIC 2	424	Systematic (crush vs culotte)	Death, MI (nonprocedural), TVR, or stent thrombosis at 6 mo	Crush 4.3% vs culotte 3.7% (P=NS)

NORDIC indicates Nordic Bifurcation Study; MI, myocardial infarction; TVR, target-vessel revascularization; CACTUS, Coronary bifurcations: Application of the Crushing Technique Using Sirolimus-eluting stents; and TVF, target-vessel failure.

CACTUS trial, in which 90% of the provisional stent procedures incorporated final kissing balloon inflations and 31% progressed to T stenting. Interestingly, however, in the CACTUS study, use of final kissing balloon inflation was associated (in the crush and provisional groups combined) with a significantly lower incidence of myocardial infarction and target-vessel revascularization. Kissing balloon success in the complex group was lower, proportionately, than in the simple group. Moreover, kissing balloon success in the crush group was lower than in the culotte group, as was found in the Nordic Bifurcation Study stent-technique trial.[23] The double-kiss crush technique has been evolved to counter this drawback[24] but adds further complexity to an already demanding procedure.

Despite the fact that many patients in the study were left with apparently significant angiographic lesions at the origin of side branches, few patients had either subsequent myocardial infarction or target-vessel revascularization. This is probably because many ostial side-branch lesions after stenting are pseudolesions. Koo et al[25] demonstrated this elegantly using fractional flow reserve, showing that only 30% of lesions that appear >75% on quantitative coronary angiography are physiologically significant.

Procedural MACE, in-hospital MACE, and in-hospital non-MACE serious adverse events all were more common in the complex group. The majority of procedural MACE was due to myocardial infarction, probably due to longer duration of vessel instrumentation with more frequent balloon and stent passage and dilation. Procedure duration, fluoroscopy time, and total x-ray dose all were greater in the complex group. This difference was seen because of the increased number of wire, balloon, and stent exchanges required in the more intricate procedures and is in keeping with data from the Nordic Bifurcation Study.[17]

Stent thrombosis was seen in relatively few cases overall, with numerically but not statistically more cases in the complex group. High-pressure stent deployment and mandatory kissing balloon inflation in dual-stented lesions probably account for the low rate of stent thrombosis compared with early studies.[11]

Study Limitations

The present study was designed as a clinical trial without angiographic follow-up, to ensure that operators did not feel obliged to aim for angiographic perfection and to ensure that lesions were not treated further after angiographic follow-up on the basis of angiographic appearance alone. The study was not restricted to true bifurcations. With present knowledge, this would have been a superior design, but the proportion of true bifurcations was >80% nonetheless. The concept of "carina shift" rather than "plaque shift" is only recent, and because atheroma is rare at the carina,[26] false bifurcation lesions have a low risk of side-branch occlusion.[27]

Additional lesions were treated in 16% of simple cases and 20% of complex cases (P=NS). These additional lesions represented a minority of cases and were equally distributed in both arms of the study. The impact of additional vessel intervention was limited by the exclusion of patients with additional complex lesions (bifurcation or type C lesions). Finally, local principal investigators had access to their own patients' data (but not those from other centers) during the conduct of the trial, and this may have led to selection bias in the trial.

Conclusions

For treatment of coronary bifurcation lesions, a systematic 2-stent technique results in longer procedures, higher x-ray doses, more procedural complications, and a higher rate of in-hospital and 9-month MACE. The provisional T-stent strategy should be the default treatment for most bifurcation lesions; however, there may be subtypes of coronary bifurcation that nonetheless merit a systematic 2-stent strategy.

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Disclosures

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CLINICAL PERSPECTIVE

Treatment of bifurcation coronary lesions generates much debate. The BBC ONE study recruited 500 patients with coronary bifurcation lesions and randomly allocated them to either a simple strategy (main-vessel stenting with or without kissing balloon dilatation/T stenting) or a complex strategy (complete lesion coverage with either crush or culotte stenting plus mandatory kissing balloon dilatation). Clinical follow-up of these 2 groups to 9 months showed an 8% major adverse event rate in the simple group versus a 15% major adverse event rate in the complex group. This difference was largely driven by periprocedural myocardial infarction. The study therefore suggests that the usual strategy for the majority of bifurcation lesions should be the simple provisional strategy and that more complex strategies should be reserved for more complex anatomies, involving perhaps large side branches with significant length ostial side-branch disease.